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Selective Heteronuclear NOE Enhancements in Benzoheterocycles. Effect of Ring Size on Indirect Three-Spin Effects

Jordi Redondo, Francisco Sánchez-Ferrando,* Montserrat Valls and Albert Virgili
Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Barcelona, Spain

The 80 MHz ^{1}H NMR and 20 MHz ^{13}C NMR spectra of five 4-methylcoumarins, six 4-methyl-2(1*H*)-quinolones and nine 3-methylbenzo[*b*]furans, including six new compounds, were fully assigned. Homonuclear ^{1}H{^{1}H} NOEs and selective heteronuclear ^{13}C{^{1}H} NOEs were measured after low-power pre-saturation of the methyl protons. Indirect, negative heteronuclear NOE enhancements were found in suitable three-spin systems of the ^{13}C–^{1}H–{^{1}H} type, and their magnitude was found to be dependent on ring size. The first examples of indirect, heteronuclear NOE enhancements on non-protonated carbons are described.

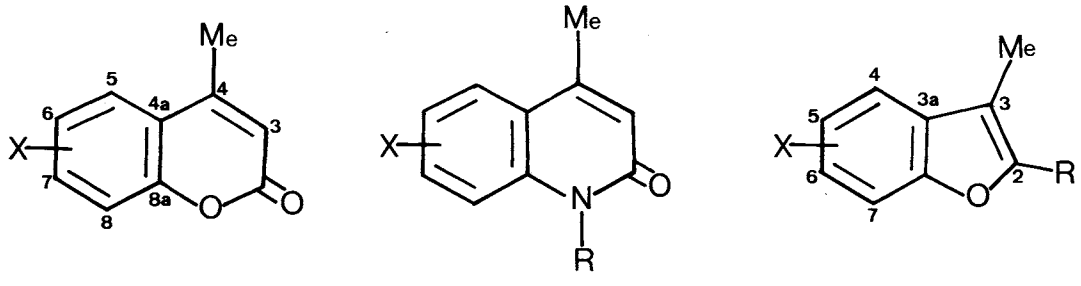
KEY WORDS Heteronuclear NOE Selective heteronuclear ^{13}C{^{1}H} NOE Indirect Negative NOE ^{13}C–^{1}H–{^{1}H} three-spin effects Coumarins 2(1*H*)-Quinolones Benzo[*b*]furans

INTRODUCTION

Considerable interest has been shown in recent years in selective heteronuclear ^{13}C{^{1}H} NOE for spectral assignment of quaternary carbons,[1] constitutional assignment of aromatic derivatives,[1–3] configurational assignment of *E*/*Z* stereoisomers[4] and conformational assignment of polycyclic derivatives.[5] In addition, intramolecular hydrogen-bonded systems have been fully characterized[1–3,6] and the effect of fluorine substituents has been explored.[6,7] In the course of these studies, indirect Overhauser enhancements (three-spin effects[8]) have been found in three-spin systems of the common ^{13}C–^{1}H–{^{1}H} type,[4,9] and in the fluorine-containing systems ^{1}H–^{19}F–{^{1}H} and ^{13}C–^{19}F–{^{1}H}.[6,7] These indirect effects are well known in the homonuclear ^{1}H–^{1}H–{^{1}H} case,[10] and their magnitude is known to be strongly dependent on the relative positions of the three nuclei involved.[8] A similar dependence on geometry applies in the heteronuclear ^{13}C–^{1}H–{^{1}H} case,[11] and its application to oligosaccharide sequencing has been explored.[12]

The 4-methylcoumarins **1–5**, 4-methyl-2(1*H*)-quinolones **6–11** and 3-methylbenzo[*b*]furans **12–20** (Fig. 1)

* Author to whom correspondence should be addressed.



1: X = 6-Cl	6: X = H,	R = Me	12: X = 5-Cl,	R = CO_2Et
2: X = 6-Br	7: X = 6-Cl,	R = H	13: X = 6-OMe,	R = CO_2Et
3: X = 6-OH	8: X = 7-Cl,	R = H	14: X = 4,6-Cl_2,	R = CO_2Et
4: X = 7-OMe	9: X = 6-Br,	R = H	15: X = 5-Cl,	R = CO_2H
5: X = 7,8-$(OH)_2$	10: X = 7-Cl,	R = CH_2Ph	16: X = 6-OMe,	R = CO_2H
	11: X = 6-Br,	R = CH_2Ph	17: X = 4,6-Cl_2,	R = CO_2H
			18: X = 5-Cl,	R = H
			19: X = 6-OMe,	R = H
			20: X = 4,6 Cl_2,	R = H

Figure 1. Structures and numbering of coumarins **1–5**, quinolones **6–11** and benzo[*b*]furans **12–20**.

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are readily available compounds which allow the easy measurement of both direct [i.e. $^{13}C\{^1H\}$] and indirect (i.e. ^{13}C–^1H–$\{^1H\}$) selective heteronuclear NOE enhancements by selective pre-saturation of the methyl protons. The large frequency separation between the ^1H NMR signals of the methyl group and the aromatic protons facilitates these determinations, without the interference of unexpected SPI effects from nearby unobserved ^{13}C satellites,[4] even using low-field electromagnet instruments. On the other hand, the distance between the irradiated methyl group and the *peri* proton (if present) should change considerably from **1–11** to **12–20**. Accordingly, the magnitude of the indirect heteronuclear NOE enhancements mediated by the *peri* proton should show a strong dependence on the size of the heterocyclic ring. The purpose of this work was to investigate this ring-size dependence.

RESULTS AND DISCUSSION

Coumarins **1–5** were prepared from the appropriate phenols and ethyl acetylacetate using the general method of von Pechmann and Duisberg.[13] Quinolones **6–9** were similarly prepared from anilines and ethyl

Table 1. 80 MHz ^1H NMR spectra of 4-methylcoumarins

		δ/ppm or substituent							J/Hz				
Compound	Solvent	3	5	6	7	8	Me	MeO	J(3, Me)	J(56)	J(57)	J(68)	J(78)
1	$CDCl_3$	6.32	7.71	Cl	7.65	7.22	2.42	—	1.2	—	2.3	—	8.5
2	$CDCl_3$	6.34	7.73	Br	7.65	7.24	2.44	—	1.2	—	2.3	—	8.5
3	MeOH-d_4	6.38	7.17	OH	7.30	7.11	2.50	—	1.2	—	2.3	—	
4	$CDCl_3$	6.12	7.48	6.81	MeO	6.86	2.39	3.90	1.2	8.7	—	2.4	—
5	DMSO-d_6	6.10	7.08	6.78	OH	OH	2.33	—	1.2	8.7	—	—	—

Table 2. 80 MHz ^1H NMR spectra of 4-methyl-2(1*H*)-quinolones

		δ/ppm or substituent								J/Hz					
Compound	Solvent	3	5	6	7	8	Me	NCH_2	Ph	J(3, Me)	J(56)	J(57)	J(67)	J(68)	J(78)
6	$CDCl_3$	6.60	7.70	7.25	7.57	7.38	2.46	—	—	1.2	8.0	1.7	7.2	1.1	8.6
7	DMSO-d_6	6.44	7.71	Cl	7.54	7.29	2.40	—	—	1.1	—	2.2	—	—	8.8
8	DMSO-d_6	6.40	7.72	7.20	Cl	7.31	2.39	—	—	1.2	8.4	—	—	1.8	—
9	DMSO-d_6	6.42	7.84	Br	7.63	7.24	2.40	—	—	1.1	—	2.1	—	—	8.6
10	$CDCl_3$	6.66	7.62	7.40	Cl	7.50	2.49	5.50	7.20	1.1	8.3	—	—	1.8	—
11	$CDCl_3$	6.70	7.80	Br	7.48	7.11	2.47	5.51	7.23	1.1	—	2.2	—	—	9.0

Table 3. 80 MHz ^1H NMR spectra of 3-methylbenzo(*b*)furans

		δ/ppm or substituent									J/Hz						
Compound	Solvent	2	4	5	6	7	Me	MeO	CH_2	CH_3	J(2, Me)	J(45)	J(46)	J(47)	J(56)	J(57)	J(67)
12	DMSO-d_6	CO_2Et	7.75	Cl	7.47	7.58	2.60	—	4.40	1.40	—	—	2.0	0.9	—	—	8.8
13	$CDCl_3$	CO_2Et	7.47	6.93	MeO	7.02	2.60	3.70	4.50	1.50	—	8.5	—	0.8	—	2.3	—
14	$CDCl_3$	CO_2Et	Cl	7.19[a]	Cl	7.38[a]	2.75	—	4.42	1.42	—	—	—	—	—	1.6	—
15	DMSO-d_6	CO_2H	7.85	Cl	7.48	7.62	2.57	—	—	—	—	—	2.0	1.0	—	—	8.7
16	DMSO-d_6	CO_2H	7.60	6.90	MeO	7.20	2.50	3.83	—	—	—	8.6	—	—	—	2.1	—
17	DMSO-d_6	CO_2H	Cl	7.40[a]	Cl	7.80[a]	2.80	—	—	—	—	—	—	—	—	1.6	—
18	$CDCl_3$	7.32	7.41	Cl	7.17	7.26	2.20	—	—	—	1.4	—	1.9	0.9	—	—	8.4
19	$CDCl_3$	7.29	7.33	6.86	MeO	6.97	2.20	3.90	—	—	1.3	8.4	—	0.7	—	2.2	—
20	$CDCl_3$	7.36	Cl	7.19[a]	Cl	7.34[a]	2.40	—	—	—	1.3	—	—	—	—	1.7	—

[a] Protons assigned by heteronuclear NOE.

Table 4. ^{13}C NMR spectra of 4-methylcoumarins

		δ/ppm										
Compound	Solvent	2	3	4	4a	5	6	7	8	8a	Me	MeO
1	$CDCl_3$	159.9	116.0	151.1[a]	121.1[b]	124.1	129.6	131.5	118.4	151.9[b]	18.4	—
2	$CDCl_3$/TFA	163.3	115.0[c]	154.3[a]	118.0[b]	127.4[c]	121.5	135.2[c]	118.9[c]	151.6[b]	18.5	—
3	DMSO-d_6	159.9	114.4[c]	152.4[a]	120.1	109.4[c]	153.7[a]	119.6	117.1	146.2[a]	17.9	—
4	$CDCl_3$	161.1	111.6[c]	152.6[a]	113.3	125.4	112.0	162.4	100.7	155.1	18.5	55.5
5	$CDCl_3$	160.2	110.2[c]	153.7[a]	112.8	115.3	112.0	149.4	132.2	143.4	18.2	—

[a] Assignment confirmed by an appropriate heteronuclear NOE experiment.
[b] Assignment confirmed by low power selective decoupling from neighbouring proton(s).
[c] Assignment confirmed by intermediate power selective decoupling from the directly bound proton(s).

Table 5. 20 MHz ^{13}C NMR spectra of 4-methyl-2(1*H*)-quinolones[a]

		δ/ppm															
Compound	Solvent	2	3	4	4a	5	6	7	8	8a	Me	NMe	NCH_2	1′	2′	3′	4′
6	$CDCl_3$	161.7	120.7[b]	146.0[c]	121.0[c]	124.8[c]	121.5	130.1	114.0[c]	139.4	18.6	28.8	—	—	—	—	—
7	$CDCl_3$/TFA	163.4	117.2	154.7[c]	122.0	124.4	131.8	132.9	119.4	134.3	19.2	—	—	—	—	—	—
8	$CDCl_3$/TFA	163.5	115.6	156.1[c]	120.7	126.9	126.4	136.4	117.5	139.3	19.5	—	—	—	—	—	—
10	$CDCl_3$	161.7	120.7[b]	146.2[c]	119.9[c]	126.1[c]	122.0	139.8	114.8[c]	136.2	18.7	—	45.5	135.7[c]	126.3	128.6	127.1
11	$CDCl_3$	161.5	121.8[c]	145.7[c]	123.0	127.5	114.9[b]	132.8	116.8[c]	137.9	18.8	—	45.5	135.9[c]	126.3	128.6	127.1

[a] The ^{13}C NMR spectrum of **9** could not be recorded because of lack of solubility, even in $CDCl_3$/TFA mixtures.
[b] Assignment confirmed by intermediate power selective decoupling from the directly bound proton(s).
[c] Assignment confirmed by an appropriate heteronuclear NOE experiment.

Table 6. 20 MHz ^{13}C NMR spectra of 3-methylbenzo[*b*]furans

		δ/ppm											
Compound	Solvent	2	3	3a	4	5	6	7	7a	Me	CO	CH_2	CH_3
12	$CDCl_3$	142.0[a]	124.5[a]	130.2[a]	120.3[a]	128.7	127.7	113.0	152.4[b]	9.0	159.8[a]	62.1	14.2
13	$CDCl_3$	140.0[a]	125.6[a]	122.1[a]	120.9[a]	112.8	160.4	95.2	155.3	9.0	160.0[a]	60.4	14.1
14	$CDCl_3$	142.0[a]	125.2[a]	124.6[a]	128.7[a]	124.5[c]	133.1	111.1[c]	154.5	10.6	159.5[a]	61.2	14.2
15	DMSO-d_6	142.8[a]	124.0[a]	130.4	121.0[a]	127.9	127.7	113.5	152.1	9.2	160.8[a]	—	—
16	DMSO-d_6	140.0[a]	124.7[a]	121.9[a]	121.6[c]	112.9[c]	160.2[a]	95.6[c]	154.9[b]	9.1	160.9[a]	—	—
17	DMSO-d_6	142.8[a]	123.5[a]	124.3[a]	127.7[a]	124.0[c]	132.1[a]	111.3[c]	153.8	9.5	160.3[a]	—	—
18	$CDCl_3$	142.7	115.3[a]	130.4	119.0	127.9	124.2	112.1	153.6	7.5	—	—	—
19	$CDCl_3$	140.4	115.9[a]	122.5	119.4	112.2	158.0	96.0	156.2	7.8	—	—	—
20	$CDCl_3$	142.8	116.1[a]	125.0	127.0	123.9[c]	129.9	110.6[c]	155.8	9.5	—	—	—

[a] Assignment confirmed by an appropriate heteronuclear NOE experiment.
[b] Assignment confirmed by low power selective decoupling from neighbouring proton(s).
[c] Assignment confirmed by intermediate power selective decoupling from the directly bound proton(s).

acetylacetate using the general method of Knorr and Combes,[14,15] and *N*-benzylquinolones **10–11** were prepared by phase-transfer-catalysed[16] benzylation of **8** and **9**. Ethyl benzo[*b*]furan-2-carboxylates **12–14** were obtained by condensation of the appropriately substituted phenol with ethyl 2-chloro-3-oxobutyrate using the general method of Boehme.[17] Subsequent saponification and copper-catalysed decarboxylation[18] in refluxing quinoline furnished acids **15–17** and benzo[*b*]furans **18–20**, respectively.

The assigned ^1H NMR spectra of coumarins **1–5**, quinolones **6–11** and benzo[*b*]furans **12–20** are given in Tables 1, 2 and 3, respectively. Only in the case of **6** was iterative simulation (LAOCOON) required, all other spectra being first order. However, the H-5 and H-7 signals of 4,6-dichlorobenzo[*b*]furans **14**, **17** and **20** could not be unambiguously assigned by standard ^1H NMR methods, including homonuclear $^1H\{^1H\}$ NOE measurements. Heteronuclear NOE measurements showed that, in all three cases, low-power pre- saturation of the downfield proton signal at $\delta_H = 7.4–7.8$ ppm resulted in a considerable (40–80%) intensity enhancement of the C-7a ^{13}C NMR signal at $\delta_C = 153–156$ ppm, thus proving the assignment to H-7 of the irradiated proton signal. This use of heteronuclear NOE for the assignment of *protons* rather than carbons can be helpful in other cases.[3]

The assigned ^{13}C NMR spectra of coumarins **1–5**, quinolones **6–8**, **10** and **11** and benzo[*b*]furans **12–20** are given in Tables 4, 5 and 6, respectively. Unambiguous assignment methods used include (i) intermediate power selective decoupling from directly attached protons (for protonated carbons), (ii) low power selective decoupling from long-range coupled protons (for some quaternary carbons) and (iii) selective heteronuclear $^{13}C\{^1H\}$ NOE measurements for other quaternary carbons.[1,4] With **3** the previously described[19] assignment of the pair of signals of C-4 and C-6 was interchanged (Table 4) on the basis of heteronuclear NOE measurements. Thus, pre-saturation of the methyl protons of **3** gave a 15.5% enhancement of the signal at $\delta_C = 152.4$ ppm and no enhancement of the signal at $\delta_C = 153.7$. Therefore, the former signal was assigned to C-4 and the latter to C-6.

Tables 7, 8 and 9 show the homonuclear $^1H\{^1H\}$ NOE enhancements of coumarins **1** and **3–5**, quinolones **6–8** and **11** and benzo[*b*]furans **12**, **13**, **15**, **16** and **18–20**, respectively, on selective pre-saturation of the methyl protons, and Tables 10–12 show the corresponding selective heteronuclear $^{13}C\{^1H\}$ NOEs.

The magnitude of both homonuclear and heteronuclear NOE enhancements showed the expected dependence on ring size. Thus, for all compounds NOE(H-*peri*{Me}) > NOE(H-*vic*{Me}), while NOE(H-

Table 7. Homonuclear NOEs of 4-methylcoumarins (irr. Me)

Compound	Solvent	%NOE(H-3)	%NOE(H-5)	%NOE(H-6)
1	$CDCl_3$	9.0	10.0	—
3	DMSO-d_6	12.0	19.0	—
4	$CDCl_3$	7.0	10.0	—
4[a]	$CDCl_3$	10.0	14.6	−3.1
5	CD_3COCD_3	2.5	8.0	[b]

[a] Results obtained at 250 MHz.
[b] Whole doublet integral vanished in the NOE difference spectrum, but the two individual lines showed opposite enhancements.

Table 8. Homonuclear NOEs of 4-methyl-2(1*H*)-quinolones (irr. Me)

Compound	Solvent	%NOE(H-3)	%NOE(H-5)	%NOE(H-6)
6	$CDCl_3$	7.0	20.5	—
7	$CDCl_3$–TFA	8.0	10.0	—
8	$CDCl_3$–TFA	8.0	11.0	—
11	$CDCl_3$	13.0	20.0	—

Table 9. Homonuclear NOEs of 3-methylbenzo[*b*]furans (irr. Me)

Compound	Solvent	%NOE(H-2)	%NOE(H-4)	%NOE(H-5)
12	CD_3COCD_3	—	11.6	—
13	CD_3COCD_3	—	5.0	—
15	DMSO-d_6	—	15.0	—
16	DMSO-d_6	—	9.0	—
18	$CDCl_3$	11.4		—
18[a]	$CDCl_3$	3.5	5.6	—
19	$CDCl_3$	—	8.2	—
20	$CDCl_3$	3.4	—	—

[a] Results obtained at 250 MHz.

Table 10. Heteronuclear NOEs of 4-methylcoumarins (irr. Me)

Compound	Solvent	%NOE C-2	C-3	C-4	C-4a	C-5	C-6
2	$CDCl_3$–TFA	—	−7.3	31.9	—	−12.9	—
3	DMSO-d_6	−15.1	−13.1	15.5	—	−15.3	—
4	$CDCl_3$	−5.2	−9.6	21.3	9.4	−9.5	—
5	$CDCl_3$	−26.3	−13.0	56.0	—	−15.4	—

Table 11. Heteronuclear NOEs of 4-methyl-2(1*H*)-Quinolones (irr. Me)[a]

Compound	Solvent	%NOE C-2	C-3	C-4	C-4a	C-5	C-6
6	$CDCl_3$	—	−6.3	37.5	11.0	−9.0	—
10	$CDCl_3$	−9.6	−14.8	46.5	13.1	−9.7	—
11	$CDCl_3$	−16.1	−10.0	27.2	—	−9.0	—

[a] Data for **7**–**9** could not be obtained because of lack of solubility.

5{Me}) (10–20%) and NOE(H-3{Me}) (7–13%) in coumarins and quinolones were larger than NOE(H-4{Me}) (5–15%) and NOE(H-2{Me}) (3–3.5%) in benzofurans (Table 9) or in similarly substituted 3-methylbenzo[*b*]thiophenes[20] (3.5–8% and 2–4%, respectively). These facts reflect the larger distance from the methyl protons to the neighbouring hydrogens (both H-*peri* and H-*vic*) in the pentagonal rings. The low values shown by dihydroxy compound **5** in hexadeuterioacetone solution (Table 7) may be due to strong solute–solvent interactions, which could decrease the molecular mobility needed in the dipole–dipole relaxation mechanism required for full NOE enhancement.

It is remarkable that, in the homonuclear case, no indirect NOEs due to three-spin effects of the ^1H–^1H–$\{^1H\}$ case were observed at 80 MHz (the data for **4** in Table 7 were obtained at 250 MHz). However, with **5**, the 80 MHz homonuclear $^1H\{^1H\}$ NOE difference spectrum (pre-saturation of the methyl protons) did show signals for both components of the H-6 doublet, although these two signals were in antiphase and the overall integral vanished. Similar antiphase behaviour has recently been observed in homonuclear ^1H–^1H–$\{^1H\}$ three-spin systems when the non-irradiated spins are strongly coupled,[21] and in heteronuclear ^1H–^{19}F–$\{^1H\}$ and ^{13}C–^{19}F–$\{^1H\}$ three-spin systems.[6,7]

Direct, positive heteronuclear NOE enhancements were observed for all quaternary carbons surrounding the C-3 methyl group of benzofuran **14** (Table 12). However, in the derived benzofuran **20** no enhancement was exhibited by C-2, now protonated and therefore relaxing preferentially with its directly attached proton H-2. The lack of indirect, negative enhancement on C-2 in **20** was attributed to the rather small value (3.4%) of the intermediate homonuclear H-2{Me} NOE in the three-spin system C-2–H-2–{Me}.

The presence of a *peri* proton at C-4 in benzofurans resulted in a net negative heteronuclear NOE enhancement of indirect origin for this carbon, ranging from −3% to −11.5% (Table 12), on pre-saturation of the methyl protons. This expected ^{13}C–^1H–$\{^1H\}$ indirect NOE contrasts with the direct, positive NOE (up to 10%) shown by the quaternary carbon C-3a in the 4,6-dichloro derivatives **14** and **20**, the only non-associating samples measured in a non-associating solvent for which this enhancement can only be of a direct origin. In all cases, the largest $^{13}C\{^1H\}$ NOEs were shown by the methyl-bearing carbon C-3.

Similarly, in coumarins **2**–**5** and quinolones **6**, **10** and **11**, the largest $^{13}C\{^1H\}$ NOEs (15.5–56%) were observed for C-4, although the enhancements were in general smaller than for the equivalent C-3 carbon in benofurans. On the other hand, indirect negative ^{13}C–^1H–$\{^1H\}$ NOEs (pre-saturation of the methyl protons) were in general larger in coumarins or quinolones than in benzofurans. Thus, NOE(C-3{Me}) in coumarins/quinolones ranged from −6.3% to −14.8% [cf. the negligible enhancement for C-2 in benzofurans **18**–**20**, unsubstituted at the 2-position (Table 12)], and there was even a sizeable negative NOE on the further removed quaternary carbon C-2 (−5.2% to −26.8%). The relatively large magnitude of both the C-2 and C-3 NOEs in these six-membered rings was attributed to the large enhancement shown by the intermediate spin H-3 in the corresponding ^{13}C–^1H–$\{^1H\}$ three-spin systems.

The H-5-mediated, negative indirect enhancements on C-5 in coumarins/quinolones (−9% to −15.4%) were also larger than the corresponding C-4 NOEs in benzofurans (−3% to −11%), as required by the shorter interproton distances involved. Again, the quaternary carbon C-4a exhibited, in general, positive enhancements (9–13%), although in some cases the poor signal-to-noise ratio prevented its accurate measurement.

Table 12. Heteronuclear NOEs of 3-methylbenzo[*b*]furans (irr. Me)

Compound	Solvent	%NOE C-2	C-3	C-3a	C-4	C-5	C-6	CO
12	$CDCl_3$	34.0	50.0	21.0	−9.4	—	—	11.0
13	$CDCl_3$	30.0	56.0	9.6	−7.1	—	—	8.3
14	$CDCl_3$	24.8	39.0	6.2	7.6	—	—	13.2
15	DMSO-d_6	40.0	62.0	—	−11.5	−9.2	—	13.0
16	DMSO-d_6	22.0	41.0	11.0	−5.0	—	—	6.3
17	DMSO-d_6	46.0	86.0	35.0	—	—	—	—
18	DMSO-d_6	−8.5	22.0	4.2	−6.7	—	—	—
18[a]	$CDCl_3$	−1.4	38.3	2.8	−3.0	—	—	—
19	$CDCl_3$	—	21.0	10.0	−6.5	—	—	—
20	$CDCl_3$	—	33.0	9.6	—	—	—	—

[a] Results obtained at 250 MHz.

CONCLUSION

The differences in the magnitude of negative, indirect heteronuclear NOE enhancements between benzo-fused pentagonal and hexagonal rings could be explained qualitatively by invoking the interproton distance in the appropriate ^{13}C–^{1}H–$\{^{1}H\}$ three-spin system. Thus, the larger distances between the methyl protons and the neighbouring H-2/H-4 hydrogens in benzofurans resulted in smaller homonuclear NOEs for these protons and, therefore, in reduced indirect heteronuclear NOEs for the attached C-2/C-4 carbons. Attempts to correlate quantitatively our heteronuclear NOE data with ring geometry, taken from published x-ray data for some benzofurans and coumarins, and using the method of Pegg *et al.*[22] for the calculation of effective distances from rotating methyl protons, have so far been unsuccessful. The heteronuclear NMR data obtained in strongly interacting solvents, such as hexadeuterioacetone, hexadeuteriodimethyl sulphoxide or mixtures of deuteriochloroform and trifluoroacetic acid, seem less reliable than those obtained in deuteriochloroform solution. Further work is in progress to overcome these difficulties.

EXPERIMENTAL

The 80 MHz ^{1}H and 20 MHz ^{13}C NMR spectra were recorded on a Bruker WP80SY spectrometer, in the FT mode, using the standard acquisition parameters.[1,2,4] and are referenced to internal TMS. The 250 MHz ^{1}H and 67.3 MHz ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer, and are also referenced to internal TMS.

Homonuclear $^{1}H\{^{1}H\}$ NOEs were determined by means of the NOE difference technique, using 5 s low-power pre-saturation, as reported elsewhere.[20] Selective heteronuclear $^{13}C\{^{1}H\}$ NOEs were determined by means of the heteronuclear NOE technique, using 20 s low-power selective proton presaturation, as previously described.[1,4] One heteronuclear NOE determination was repeated eight times, and the results were found to be reproducible to within $\pm 3.5\%$ (relative).

1-Benzyl-7-chloro-4-methyl-2(1*H*)-quinolone (10)

7-Chloro-4-methyl-2(1*H*)-quinolone (**8**)[15] (250 mg, 1.3 mmol) was added to a stirred suspension of finely divided NaOH (186 mg, 4.6 mmol), K_2CO_3 (372 mg, 2.7 mmol) and n-$Bu_4N^+HSO_4^-$ (44 mg, 0.13 mmol) in anhydrous benzene (15 ml). The mixture was boiled under reflux and a solution of benzyl chloride (245 mg, 1.9 mmol) in anhydrous benzene (5 ml) was slowly added. After refluxing for 6 h, addition of benzene, washing with water to neutrality and solvent removal yielded **10** (290 mg, 80%), m.p. 132–135 °C, IR (KBr): 3020, 2960, 1630, 1570, 1440, 1410, 1380, 1320, 910, 850 and 710 cm^{-1}, 80 MHz ^{1}H NMR: see Table 2. 20 MHz ^{13}C NMR: see Table 5. Elemental analysis: found, C 71.50, H 5.26, N 4.45%; $C_{17}H_{14}ClNO$ requires C 71.96, H 4.97, N 4.94%.

1-Benzyl-6-bromo-4-methyl-2(1*H*)-quinolone (11)

This compound was similarly obtained from 6-bromo-4-methyl-2(1*H*)-quinolone (**9**)[15] and benzyl chloride in 80% yield; m.p. 128–129 °C (from tetrachloromethane), IR (KBr): 3100, 1670, 1620, 1600, 1440, 1315, 900, 830 and 745 cm^{-1}. 80 MHz ^{1}H NMR: see Table 2. 20 MHz ^{13}C NMR: see Table 5. No correct elemental analysis could be obtained for this compound.

Ethyl 5-chloro-3-methylbenzo[*b*]furan-2-carboxylate (12)

To a stirred suspension of benzene-washed sodium hydride (10.9 g of a 55% dispersion in mineral oil, 0.25 mol) in anhydrous benzene (250 ml) was added dropwise 4-chlorophenol (32.8 g, 0.25 mol). After additional stirring for 10 h the mixture was refluxed for 30 min. After cooling to room temperature ethyl 2-chloro-3-oxobutyrate (35.5 ml, 0.25 mol) was added and the mixture was again refluxed for 10 h. After cooling, washing with water (3 × 125 ml) and drying (anhydrous sodium sulphate), the solvent was eliminated and the residue was distilled *in vacuo*. The distillate was identified as 4-chlorophenol (b.p. 70–100 °C/0.9 mmHg), and the residue, a brown oil, as crude ethyl 2-(4-chlorophenoxy)-3-oxobutyrate (31.31 g, 48.8%), pure enough for the next step.

Polyphosphoric acid was prepared by addition of 50 ml of 85% aqueous phosphoric acid to 100 g of P_2O_5 with stirring and heating for 8 h at 130 °C. The resulting viscous oil was cooled to 90 °C and 31.31 g (0.118 mol) of the above crude ethyl 2-(4-chlorophenoxy)-3-oxobutyrate were slowly added. The mixture was heated at 110 °C for 2 h and then cooled to room temperature. Water (400 ml) was cautiously added with vigorous stirring and the mixture was extracted with chloroform (4 × 125 ml). The combined extracts were washed with water (125 ml) and saturated sodium hydrogen carbonate solution (125 ml). After drying (anhydrous sodium sulphate), solvent removal yielded a solid which was recrystallized from chloroform–hexane, affording 17.9 g (61.5%) of **12**, m.p. 83–84 °C. IR (KBr), 3070, 2970, 2920, 1700, 1580, 1430, 1370, 1340, 1300, 1265, 1205, 1140, 1100, 1010, 890, 845 and 820 cm^{-1}. MS (70 eV): m/z 240 (28%), 238 (M^+, 94), 210 (63), 193 (35), 165 (60), 136 (31) and 101 (100), 80 MHz ^{1}H NMR: see Table 3. 20 MHz ^{13}C NMR: see Table 6. Elemental analysis: found, C 60.33, H 4.67, Cl 14.84; $C_{12}H_{11}ClO_3$ requires C 60.38, H 4.65, Cl 14.85%.

Ethyl 4.6-dichloro-3-methylbenzo[*b*] furan-2-carboxylate (14) and 4,6-dichloro-3-methylbenzo[*b*]furan (20)

Sodium 3,5-dichlorophenoxide (from 3,5-dichlorophenol and sodium hydride in benzene) and ethyl 2-chloro-3-oxobutyrate were refluxed in benzene as above for 50 h. Vacuum distillation of unreacted ethyl 2-chloro-3-oxobutyrate and chromatography of the

residue on silica gel, eluting with hexane–dichloromethane mixtures, furnished crude ethyl 2-(3,5-dichlorophenoxy)-3-oxobutyrate (24%) as an oil. Reaction of this oil with polyphosphoric acid as above and chromatography of the reaction product on silica gel, eluting with hexane–dichloromethane mixtures, gave two compounds.

The first compound eluted (10%) was **20**, m.p. 69–71 °C. IR ($CHCl_3$): 3000, 2950, 2920, 1700, 1610, 1560, 1450, 1390, 1330, 1305, 1090, 940 and 840 cm^{-1}. MS (70 eV): *m/z* 204 (10%), 202 (56), 200 (M^+, 100), 199 (83), 165 (20), 136 (16). 80 MHz ^1H NMR: see Table 3. 20 MHz ^{13}C NMR: see Table 6. Elemental analysis: found, C 53.75, H 2.72; $C_9H_6Cl_2O$ requires C 53.76, H 3.01%.

The second compound eluted (64%) was **14**, white needles, m.p. 70–72 °C (hexane), IR ($CHCl_3$) 2980, 1700, 1685, 1450, 1445, 1365, 1340, 1270, 1230, 1190, 1140, 1070, 965 and 835 cm^{-1}. MS (70 eV): *m/z* 276 (12%), 274 (65), 272 (M^+, 100), 244 (81), 227 (37), 200 (22), 171 (14) and 136 (37), 80 MHz ^1H NMR: see Table 3. 20 MHz ^{13}C NMR: see Table 6. Elemental analysis: found, C 52.72, H 3.59, Cl 25.82; $C_{12}H_{10}Cl_2O_3$ requires C 52.78, H 4.36, Cl 25.96%.

4,6-Dichloro-3-methylbenzo[*b*]furan-2-carboxylic acid (17)

A mixture of 440 mg (1.6 mmol) of ester **14** and 30 ml of 10% aqueous KOH was stirred under reflux for 6 h. After cooling to 80 °C, concentrated HCl (8.1 ml) was added. The precipitate was recrystallized from methanol, yielding 250 mg (64%) of **17**. This acid sublimed without melting at 216–218 °C. IR (KBr): 3100–2500, 1680, 1575, 1430, 1370, 1320, 1270, 1245, 1165, 960, 840 and 815 cm^{-1}. MS (70 eV): *m/z* 248 (5%), 246 (28), 244 (M^+, 44), 201 (8), 199 (14), 172 (6), 170 (5), 45 (100). 80 MHz ^1H NMR: see Table 3. 20 MHz ^{13}C NMR, see Table 6. No correct elemental analysis could be obtained for this compound.

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